A NOVEL METHOD TO CHARACTERIZE SMALL ABSORBERS IN TURBID MEDIA WITH A PRIORI ULTRASOUND INFORMATION

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The objective of this study is to improve the performance our ultrasound/NIR combined imager for breast cancer detection.

Near infrared diffusive imaging has shown a promising future for breast cancer detection. Currently, most forward models digitize the volume under investigation into 3-D voxels and relate changes in optical properties in each voxel to the perturbation of each detected signal. This approach generally needs extensive computation and causes problems in image reconstruction, as the number of unknown parameters well exceeds the number of measurements. Our approach is based on the fact that tumors are confined in isolated regions surrounded by normal tissues, which are assumed homogeneous. Instead of a voxel-based representation, we characterize those targets in terms of their center locations, volumes, and optical properties. The total number of these parameters is far less than the total number of imaging voxels with unknown optical properties. With the target center location information estimated from co-registered ultrasound images, optical inhomogeneities can be represented by their moments up to the second order. The absorption coefficient of each embedded target can be determined accurately by reconstructed moments and, when the signal to noise ratio is low, by using ultrasound volume information. A simple nonlinear correction formula is incorporated to reduce errors caused by using linear perturbation models. For a small sphere (0.5 cm^3) of absorption coefficient 0.288 cm-1 above the background, the reconstruction accuracy has been improved from 60% to 84% when nonlinear correction is used. Results from phantoms and excised tumors will be presented.

In conclusion, in this paper, a novel moment-based reconstruction method for characterizing heterogeneities inside a homogeneous background is proposed and evaluated through simulations and experiments. A simple formula that accounts for nonlinear terms beyond the Born approximation is incorporated into the method. In comparison with current sophisticated NIR image reconstruction algorithms, our method is very simple and robust.

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EXCITATION-ENHANCED IMAGING FOR IMPROVED BREAST CANCER DETECTION

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Ultrasound is currently an auxiliary modality in breast imaging used mainly to differentiate between cystic and solid lesions. Investigations into the possibility of breast cancer diagnosis based on Doppler ultrasound flow detection have produced mixed results, due to overlap between flow measurements in benign and malignant tumors. One problem may be the lack of sensitivity in flow detection in small tumor vessels. Ultrasound contrast agents increase the echo intensity of blood flow signals up to 30 dB especially when combined with new contrast imaging modalities such as harmonic imaging. However, harmonic imaging has been found to suffer from reduced blood-to-tissue contrast resulting from second harmonic generation and accumulation in tissue. Instead, we propose using a patented multi-pulse contrast imaging technique, which applies two acoustic fields one for bubble excitation and the other for imaging. The excitation field will momentarily increase bubble sizes resulting in an increase in the number of bubbles with a size close to the resonance size corresponding to the (second) imaging field. If the imaging field is applied simultaneously with (or slightly after) the excitation field, acoustic scattering from bubbles around resonance size becomes markedly stronger than without the excitation field.

In vitro an 8mm vessel embedded in a tissue-mimicking flow phantom (ATS laboratories, Bridgeport, CT) was imaged at a low MI of 0.2 in both fundamental (3.0 MHz) and harmonic (2.5/5.0 MHz) grayscale modes with a curvilinear transducer connected to a PowerVision 7000 scanner (Toshiba America Medical Systems Inc, Tustin, CA). Excitation pulses (0.5-2.0 MHz, 2-16 cycles and 0.4-2.0 MPa) were produced by a single-element large-aperture transducer positioned at a 45° angle intersecting the imaging plan and the vessel. Diluted suspensions of ultrasound contrast agents were pumped through the flow system. Images were digitized before and after transmission of excitation pulses for video intensity measurements. In vivo the aorta of 2 rabbits was imaged using a similar setup.

While video intensities of scattered signals from the surrounding tissue were unchanged, video intensities of echoes from contrast within the vessel were markedly enhanced in both fundamental and harmonic mode. Optimal enhancements of 12 dB in the fundamental mode and 18 dB in the harmonic mode were achieved in vitro using 16-cycle excitation pulses with a center frequency of 0.53 MHz. In vivo, 4 dB of enhancement within the aorta was seen following a 1 MHz, 16-cycle excitation pulse.

In conclusion, multi pulse contrast imaging produces marked enhancement in the contrast-to-tissue image contrast in both fundamental and harmonic mode. This unique ultrasound contrast modality may significantly improve the sensitivity of currently known breast imaging modalities.

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CONTRAST-ENHANCED SUBHARMONIC ULTRASOUND IMAGING

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Ultrasound imaging is currently an auxiliary modality in breast imaging. It is mainly used to differentiate between cystic and solid lesions. Investigations into the possibility of breast cancer diagnosis based on Doppler ultrasound flow detection have produced mixed results, due to overlap between flow measurements in benign and malignant tumors. One problem may be the lack of sensitivity in flow detection in small tumor vessels using ultrasound. Ultrasound contrast agents produce increases of 15 to 25 dB in the echo intensities of blood flow signals; especially when combined with new contrast-specific imaging modalities such as harmonic imaging. However, harmonic imaging has been found to suffer from reduced blood-to-tissue contrast resulting from second harmonic generation and accumulation in tissue. As an alternative we propose using subharmonic imaging (SHI) by transmitting at the double the resonance frequency ($2f_o$) and receiving at the subharmonic (f_o). SHI has the potential to detect slow, small volume blood flow associated with tumor neovascularity, making early detection and identification of tumors very likely. Hence, the current project proposes to increase the ability of breast ultrasound to differentiate between benign and malignant lesions by using SHI.

Initial experiments were set up to detect subharmonic signal components generated by contrast bubbles flowing through thin tubes (diameter: 300 ± 25 μm, wall thickness: about 6 μm and a tube with diameter 1 mm ± 25 μm and similar wall thickness). A dual transducer setup, with an angle of 40º between transducers, was used for transmitting and receiving pulsed wave ultrasound. A pulse generator was used to generate 4 MHz, 32 cycle bursts with PRF's between 20 and 100 Hz. This signal was amplified to generate the desired pressure levels (0.3 – 1.5 MPa) to be transmitted to the thin tube embedded in a tissue mimicking phantom. The contrast agent used for the study was Optison (Amersham Health, Oslo, Norway), which has a resonance frequency of 2 MHz. Received signals were sampled at 40 MHz and 32 individual traces were averaged before calculating the power spectrum.

Subharmonic signal could be observed over a frequency range of about 1.9 to 2.1 MHz, with the peak signal at half the insonation frequency of 4 MHz. The amplitude of the subharmonic backscatter was about 10 dB higher than the corresponding signal from distilled water, when the power of insonation was 1.5 MPa.

In conclusion, experiments show that sufficient subharmonic backscatter is generated by bubbles in vessels comparable in size to the ones formed during breast tumor angiogenesis. Using suitable instrumentation, this information may be used for early detection of malignant breast tumors.

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EVALUATION OF DIFFRACTIVE ULTRASOUND FOR REAL-TIME BREAST IMAGING AND BIOPSY GUIDANCE

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Despite recent advances in the development of complementary approaches to breast mammography, breast cancer remains a prevalent and devastating disease. Generally, new advances fail to provide real-time, large field of view, high-resolution approaches to breast imaging where both early detection and subsequent management of breast disease are primary targets. This study evaluated a promising approach to breast imaging which uses Diffractive Ultrasound (DU) imaging developed by Advanced Imaging Technologies, Inc.

Methods were developed to evaluate prototype modifications to improve DU image quality and system adaptations specifically for breast imaging. Changes to acoustic and optical chain components, and patient and operator interfaces were evaluated along with preliminary image post processing algorithms. Ten normal and ten diagnostic group volunteers were studied to resolve procedural aspects of image data collection, acquire data for a range of breast sizes and types, examine robustness of processing algorithms, and gain experience in image interpretation. To explore other DU applications in breast healthcare, biopsy techniques employing approach guidance in combination with real-time needle visualization were investigated.

The evaluation methods were implemented as standard procedures for quantifying DU system performance and acquiring breast images. Human studies show that DU has particular strength in differentiating soft tissue structures particularly in women with dense breast composition, and in identifying boundaries and texture with strong diffractive components. Simulated biopsy data indicate that physicians without prior DU operational experience were successful in acquiring simulated targets embedded in biopsy phantoms.

There will be obvious benefits to low cost imaging systems that are successful in early detection of breast disease and demonstrate an improved ability to monitor the progression of breast disease non-invasively. Results indicate that DU has a high potential to detect and differentiate breast lesions without the use of ionizing radiation or painful compression. DU also shows promise in biopsy guidance and may become an important alternative to more invasive, open surgical biopsies or time consuming stereotactic procedures.

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NOVEL ULTRASOUND SENSOR AND RECONSTRUCTION ALGORITHM FOR BREAST CANCER DETECTION

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Mammography is currently used for screening women over the age of 40 for breast cancer. It has not been used routinely on younger women because their breast composition is mostly glandular, or radiodense, meaning there is an increased radiation exposure risk as well as a high likelihood of poor image quality. For these younger women, it is calculated that the radiation exposure risk is higher than the potential benefit from the screening. It is anticipated that transmission ultrasound will enable screening of much younger women and complement mammographic screening in women over 40.

Ultrasonic transmission tomography holds out the hope of being a discriminating tool for breast cancer screening that is safe, comfortable, and inexpensive. From its inception, however, this imaging modality has been plagued by the problem of how to quickly and inexpensively obtain the data necessary for the tomographic reconstruction.

The objectives of this project were: to adapt a new kind of sensor to data acquisition for ultrasonic transmission tomography of the breast, to collect phantom data, to devise new reconstruction algorithms to use that data, and to recommend improved methods for displaying the reconstructions.

The ultrasound sensor images an acoustic pressure wave over an entire surface by converting sound pressure into an optical modulation. At the beginning of this project the sensor imaged an area of approximately 7 mm by 7 mm and was very fragile. During the first year of this research we improved the robustness of the sensors so they now last indefinitely. Our task for the second year was to enlarge the sensor aperture. Due to material limitations, we were not able to enlarge our original design.

We used the sensors to collect data from a small phantom of monofilament fishing lines. We were able to use both established (diffraction tomography) and new (paraxial adjoint method tomography) reconstruction techniques to generate 3D images of the phantom.

We also investigated techniques for displaying the reconstructions in ways that are readily comprehensible by physicians. Use of specific color densities and background grids was found to be most efficacious.

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PRELIMINARY RESULTS OF A NEW METHOD OF 3D ULTRASOUND CONTRAST AGENT MAPPING OF VASCULAR ANOMALIES FOR CHARACTERIZATION OF BREAST MASSES

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Doppler ultrasound and other imaging modalities have been used to assess characteristics of vasculature associated with malignant breast masses. Specific to our institution, promising results have been achieved in discriminating benign from malignant masses using Doppler vascularity measures in conjunction with ultrasound grayscale features. In addition to characterization, co-registration of sequential image volumes of malignant masses for sequential assessment chemotherapy treatment has been undertaken by our group.

The purpose of this work is to develop an innovative dual-transducer method to control the destruction and imaging of ultrasound contrast during 3D ultrasound scanning of suspicious breast masses. This method, which involves sequential scanning and co-registration of image volumes acquired during contrast refill, should provide mapping of vascularity around these masses and highlight the associated anatomic variation in mean transit time.

Progress of the construction and testing of the mechanical, electrical, and software components of the scanning apparatus are presented here. Eventually, this new imaging scheme will be evaluated in a small patient population to begin to establish the refill characteristics for a variety of suspicious breast masses, and appropriate mathematical models will be developed to characterize contrast agent refilling following destruction specific to the dual-transducer system. Experimental assessment of contrast agent life-span, destruction characteristics, and refill imaging has been undertaken in flow phantoms. The feasibility of producing accurate 3D refill maps will be evaluated, and a software system will be developed to visualize quantification of regional perfusion in and around the region of interest. Preliminary results are presented here.

The innovative technique currently in development may allow rapid 3D imaging of the refill rate and may also prove effective in imaging small slow-flow microvasculature. This may be particularly relevant in the detection of vascular anomalies associated with angiogenesis near new tumor growth, which in turn would likely improve the ability of ultrasound in discriminating benign from malignant breast masses as well as broaden existing knowledge of tumor physiology.

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A TRANSMISSION ULTRASOUND BASED ON THE PIEZOELECTRIC SENSING CCD AND ITS POTENTIAL FOR IMAGING THE BREAST

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A transmission ultrasound system using C-scan geometry has been constructed based on a patented hybrid microelectronic array that is capable of generating ultrasound images with fluoroscopic presentation. The array is made up of two components, a silicon detector/readout array and a piezoelectric material that is deposited onto the array through semiconductor processing. The array is 1 cm on a side consisting of 128×128 pixel elements with 85μm pixel spacing. The energy that strikes the piezoelectric material is converted to an analog voltage that is digitized and processed by a standard commercial video electronics.

To generate real-time images, ultrasound is introduced into the object under study with a large unfocused plane wave source. The resultant pressure wave strikes the object and is attenuated and scattered. The device detects scattered as well as attenuated ultrasound energy which allows the use of an acoustic lens to focus on detected energy from an object plane. The acoustic lens collects the transmitted energy and focuses it onto the ultrasound sensitive array. Therefore, a circular area covering 3 inches in diameter can be imaged onto the microarray.

The images generated by the device appear with no speckle artifact with fluoroscopy-like presentation. The images show no obvious geometrical distortion. The experimental results indicated that the system has a spatial resolution of 0.32 mm. It can resolve 3mm simulated breast lesions with low differential contrast and an attenuation coefficient difference less than 0.07 dB/cm/MHz. Phase contrast of the lesion objects is also clearly visible. We have also implemented an image restoration filtering technique in Fourier domain to enhance the sharpness of the image. Based on this prototype, we have demonstrated a procedure for image guided breast biopsy. In addition, punctured needle tracks in a tumor were clearly observed. This implies the potential of observing the spiculation of masses in vivo.

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IN VIVO IMAGING OF ULTRASONIC ANGULAR SCATTER

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Ultrasonic imaging has many strengths including real-time frame rates, high spatial resolution, excellent soft tissue contrast, and relatively low cost. Ultrasound does however suffer from a number of limitations. The most notable of these is the lack of adequate image contrast for certain clinically relevant targets, such as microcalcifications.

We have invented and implemented a novel imaging method which uses a modified clinical imaging system to interrogate a new source of tissue contrast, namely ultrasonic angular scatter variations. Our approach retains all the advantages of ultrasonic imaging, but opens new avenues of application by offering a new source of contrast.

In the context of ultrasound, angular scatter refers to variations in the amplitude and phase of the echoes received as the angle between the transmit and receive transducers is altered. Angular scatter was first investigated in the mid 1980s using awkward custom experimental systems. While these systems yielded some insight, they were clinically impractical and required averaging over hundreds of acquisitions to produce meaningful angular scatter profiles.

We have developed a new method of angular scatter data acquisition that is not only clinically practical, but which provides reliable angular scatter profiles at each location without averaging. These local angular scatter profiles can be processed in a number of ways to yield angular scatter images. We obtain the angular scatter profiles by shifting the transmit and receive apertures in equal and opposite directions while repeatedly interrogating the same location. This approach is implemented on a phased array system so that all translation is performed electronically and data is acquired in real-time.

We present results from human subjects and tissue mimicking phantoms indicating that angular scatter imaging offers information unavailable in conventional ultrasound images. In phantoms we show that angular scatter imaging can differentiate targets which appear identical in conventional ultrasound. In other phantoms we show significant improvements in the contrast of microcalcification mimicking targets. In human subject we show that angular scatter offer a novel source of contrast which is independent of conventional image contrast.

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DETECTION OF MICROCALCIFICATIONS UTILIZING SONOGRAPHY COUPLED WITH POWER DOPPLER AND ACOUSTIC RESONANCE

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Ductal carcinoma in situ (DCIS) represents the earliest form of breast cancer. Even though other imaging modalities may be utilized in the evaluation of breast abnormalities, currently, mammography is the only reliable method in detecting microcalcifications. Our goal with this project was to evaluate the efficacy of ultrasonography coupled with acoustic resonance imaging (ARI) in the evaluation of microcalcifications.

Gelatin phantoms and tissue phantoms, made from turkey breast, were imbedded with calcium carbonate particles. Patients, who were undergoing breast biopsy for microcalcifications, were recruited for the study. Imaging was performed using gray scale and power Doppler coupled with ARI. The phantoms and the patients were scanned in the B-scan mode and the power Doppler mode while the particles were resonated between 50-500 Hz. The visualized calcium carbonate particles in the phantoms were cored biopsied using a 14-gauge needle. The patients subsequently underwent needle localization and excisional biopsy or had stereotactic core needle biopsy of the microcalcifications.

The specimen radiographs from the core needle biopsy of the phantoms showed the calcium carbonate particles within the specimen indicating that the area detected on power Doppler and ARI correlated to the calcium particles. Thus far, we have sonographed 10 patients with benign microcalcifications and 8 patients with malignant microcalcifications. In all cases, significant enhancement was observed in the expected region of the calcifications between 200-300 Hz. There was also, however, enhancement of secondary structures associated with connective tissues of the breast.

We conclude that calcium carbonate particles can be detected using power Doppler sonography coupled with ARI in phantoms. Thus far in patients, enhancement may be seen in the region of the calcifications but there is also enhancement of surrounding secondary structures. The ability to visualize microcalcifications using sonography will enhance the detection and evaluation of the earliest form of breast cancer, DCIS, allowing for improved evaluation without exposing the patients to additional radiation.

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BREAST LESION DIAGNOSIS USING COMBINED NEAR-INFRARED DIFFUSIVE LIGHT AND ULTRASOUND: INITIAL CLINICAL RESULTS

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The objective of this study is to validate a novel imaging instrument and method using co-registered optical and ultrasound images to improve current breast cancer diagnosis.

We will present our initial clinical results obtained with a novel combined ultrasound and optical imaging scanner. The scanner is capable of providing simultaneous ultrasound and optical imaging and lesion characterization. Five cases of infiltrating carcinomas, a fibroadnoma, a complex cyst, and a simple cyst are analyzed in detail and optical parameters of these five lesions are correlated with ultrasound findings. Biopsy resutls are used as "gold" standard. In one infiltrating carcinoma case, high optical absorption at wavelength of 780 nm and low absorption at 830 nm were obtained, and the lesion was highly deoxygenated. In another infiltrating carcinoma case, low optical absorption at 780 nm and high optical absorption at 830 nm were obtained and the lesion was highly oxygenated. The optical oxyhemoglobin image map of the second carcinoma case revealed that the highly oxygenated areas were at boundary of the lesion which may indicate significant developments of blood vessels at the periphery of the cancer. In the fibroadenoma case significant purturbations of amplitude and phase of optical signals were measured and high optical absorption coefficients were obtained at both wavelengths. For the cyst cases, the optical purturbations measured in lesion regions were similar to those measured in normal contralateral breasts and the estimated reduced optical scattering coefficients in lesion regions were less than those obtained in the normal breasts. This result was sound because cysts scatter less than normal breast tissue.

In conclusion, our initial results indicate that infiltrating carcinomas may have significant wavelengh dependent optical absorption changes, while the other benign lesions demonstrate wavelength independent absorption changes. Currently, more patients are recruited to this study, and the predictive power for identifying malignancies by the use of the combined technique will be assessed.

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